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by Afif Nurul Hidayati

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The Varicella-Zoster Virus Vaccines : Benefits and Risks

Afif Nurul Hidayati
Department of Dermatology and Venereology, Faculty of Medicines, Universitas Airlangga/
Dr. Soetomo General Hospital/ Universitas Airlangga Hospital
Surabaya, Indonesia

ABSTRACT

Varicella (chickenpox) and herpes zoster (shingles) are distinc clinical entities caused by *Varicella-zoster virus* (VZV). Varicella is a highly contagious exanthema that occurs most often in children. In normal children, systemic symptoms are usually mild and serious complications are rare. In adult and immunologically compromised persons, varicella is more likely to be associated with life-threatening complications. Herpes zoster (HZ) is a viral disease characterized by a dermatologic and neurologic involvement caused by the reactivation of the latent varicella zoster virus (VZV) acquired during primary infection (varicella). HZ incidence increases with age and is related to waning specific cell-mediated immunity (CMI). Pain is an important clinical manifestation of herpes zoster, and the most common debilitating complication is chronic pain or post-herpetic neuralgia (PHN) characterized by chronic pain lasting at least 30 days, with impact on patients' quality of life. Available treatments are quite unsatisfactory in reducing pain and length of the disease. The evaluation of the epidemiology, the debilitating complications of varicella and HZ, the sub-optimal available treatments and the costs related to the diagnosis and clinical/therapeutic management of varicella and HZ patients have been rationale for the search of an adequate preventive measure against these diseases. The use of varicella vaccine reduces the incidences, hospitalization, and complications of varicella. Zoster vaccine reduces the incidence of herpes zoster by one-half and the incidence of PHN by two-thirds. Clinical studies show a good level of efficacy and effectiveness, particularly against the burden of illness and PHN in all age classes. Herpes zoster vaccine is needed for older person to reduce the incidences, hospitalization, and complications of herpes zoster, especially PHN.

Key words: varicella, herpes zoster, *Varicella-zoster virus*, PHN, vaccine, benefits, risks.

INTRODUCTION

Varicella (chickenpox) and Herpes zoster (HZ/shingles) are infectious diseases caused by *Varicella-zoster virus* (VZV) which is a family of *Herpesviruses*. Varicella provides an overview of the highly contagious acute eczema that often occurs in children, due to primary VZV infection in susceptible individuals. HZ occurs due to the latent reactivation of VZV especially in neuronal cells and sometimes within the dorsal root ganglion cells and sensory nerve ganglion of the cranial nerve, spreading to dermatomes or neural networks corresponding to the innervated segment. Herpes zoster (HZ) often occurs in immunocompromised patients and individuals.[1,2,3]

In normal children, systemic symptoms are usually mild and serious complications are rare. In adult and immunologically compromised persons, varicella is more likely to be associated with life-threatening complications. Herpes zoster is most common in older adults and immunosuppressed individuals. Pain is an important clinical manifestation of herpes zoster, and the most common debilitating complication is chronic pain or post-herpetic neuralgia (PHN) characterized by chronic pain lasting at least 30 days, with impact on patients' quality of life. Available treatments are quite unsatisfactory in reducing pain and length of the disease. The evaluation of the epidemiology, the debilitating complications (PHN), the sub-optimal available treatments and the costs related to the diagnosis and clinical/therapeutic management of HZ patients have been he rationale for the search of an adequate preventive measure against this disease, such as varicella-zoster virus vaccines.[1,2,3]

REVIEWS

Varicella is a highly contagious disease, occurs worldwide, but is more common in children and in high temperate areas.[1,2] In Europe and North America before the era of vaccination, 90% of cases occur in children under 10 years of age, and less from 5% at over 15 years of age. In 1988-1995, nearly 11,000 patients needed admission to hospital, and 100 deaths occurred each year in the United States.[1] The high number of varicella in Indonesia is evidenced by Jufri and colleagues in 1995-1996 who prove that two-thirds of the 15-year-old population got antibodies to VZV.[3] The risk of death is higher in infants and adults than in children. Vulnerable health workers have significant potential for nosocomial varicella transmitted infection. [1]

VZV is a family of *Herpesviruses*. Other viruses belonging to *Herpesvirus* are *Herpes simplex virus type 1* (HSV-1) and *type 2* (HSV-2); *Cytomegalovirus* (CMV); *Epstein-Barr virus* (EBV); *Human herpesvirus-6* (HHV-6) and HHV-7 causing roseola; and Kaposi's sarcoma-associated *herpesviruses* called HHV-8.[1,2] All *Herpesviruses* have the ability to cause latent infection that persists throughout life.[1,2]

The incubation period of varicella averaged 14-15 days (ranging from 10-23 days). The incubation period may be prolonged in individuals who have received passive immunization with varicella-zoster immune globulin (VZIG) or zoster immune plasma (ZIP), or after exposure to varicella vaccine immunization live attenuated Oka strain.[1] Varicella is acquired or transmitted primarily through the respiratory tract, but infection can also spread by direct contact. After entering through

the upper respiratory tract mucosa and oropharynx, the virus multiplies, infecting T cells in the tonsils, spread through the blood and lymph glands (primary viremia). Infected T cells carry the virus to the reticuloendothelial system, replicate again, and towards the skin. Natural immune responses prevent VZV replication and rash formation.[1] The incubation period involves natural defenses (interferon, NK cells) and specific immune responses. About 2 weeks secondary viremia occurs and symptomatic symptoms and a successive skin lesion, depicting cyclic viremia develop, which stops within 3 days.[1]

"Natural" varicella usually provides immunity throughout life. Repeated exposure increases the response of humoral and cellular immunity. In immunocompromised conditions, there has been documented reinfection that manifests clinically as varicella in general. “Modified” varicella, for example, infection occurs early in a baby's life that is still affected by the antibody effect of the mother, or individuals who have been given live attenuated varicella vaccine, VZV exposure may provide a second but usually mild clinical manifestation.[1] Varicella rarely complicates normal children. The most frequent complications are secondary infection due to bacteria, usually *Staphylococci* or *Streptococci* in the form of impetigo, furuncle, cellulitis, erysipelas, and gangrene (rare). Local infections often cause scarring. Although rare, septicemia can occur due to the spread of infection. The bullae may occur in the case of superinfection of *Staphylococci* producing exfoliative toxins.[1,2] In non-vaccinated children, one-third develop an invasive *Streptococcal group A* infection. Vaccination significantly reduces the infection.[1] Secondary pneumonia due to bacteria, otitis media, suppurative meningitis are rare complications in children but often in adults, and usually have a good response to antibiotics, but can be fatal in leukopenia patients. In children, fever and constitutional symptoms are rare, fewer rashes, complications less common than adults. Mortality of adult patients due to primary pneumonia due to velocities of about 10-30%.[1] Varicella during pregnancy is treated for the mother and fetus. The fetus may die from premature birth or due to maternal death from severe pneumonia. Maternal viremia can cause congenital abnormalities. Perinatal varicella (varicella occurring within 10 days of birth) is more fatal than varicella in infants due to infection several weeks after birth.[1] Mortality and morbidity of varicella are elevated in immunocompromised patients, more severe, longer, and potentially systemic complication. Immunosuppressed patients or glucocorticoid-treatment patients may develop into pneumonia, encephalitis, and hemorrhagic complications (mild to severe and fatal febrile purpura called "malignant" varicella), CNS complications include Reye syndrome (acute encephalopathy with fatty liver degeneration), acute cerebral ataxia, hepatitis, myocarditis, glomerulonephritis, orchitis, pancreatitis, gastritis, arthritis, Henoch-Schonlein vasculitis, optic neuritis, keratitis, and iritis.[1,2]

The occurrence of HZ is independent of the prevalence of varicella, and there is no evidence that HZ can be obtained through contact with varicella or HZ patients. The incidence of HZ is determined by several factors that affect the relationship between host and virus.[1] HZ is rare in neonates and children, if it is usually mild, healed without any residual symptoms.[3] A strong risk factor is old age. In Europe and North America the incidence of HZ in the general population is 1.5-3.0 per 1,000 person-years and 7-11 per 1,000 per year in individuals aged ≥ 60 years. The incidence of PHN also increased in the elderly.[1] In 2011-2013, from a total of 2232 HZ patients in 13 Teaching Hospitals in Indonesia, the peak of HZ cases occurred at the age of 45-64 years and more commonly found in women.[3] In Dr. Soetomo Hospital, in 2010-2013 there were herpes zoster patients aged 0-4 years, while 5-14 years were 8 patients (8.8%), 15-24 years were 15 patients (12.7%), 25-44 years were 21 of patients (17.8%), peak age of HZ patients was 45-64 years (40.7%), aged ≥60 years were 26 patients (22.0%).[4] Another important determinant factor was cellular immune dysfunction. Patients with immunosuppression (HIV infection, bone marrow transplant, leukemia, lymphoma, cancer chemotherapy, corticosteroids treatment) have 20-100 times greater risk of HZ than immunocompetent individuals. Other factors are women, physical trauma to the skin, surgery, psychological stress, IL-10 gene polymorphism, and whites. In children, exposure and contact with varicella increase VZV-CMI and provide protection against HZ. The second episode of HZ is not common in immunocompetent individuals, and the third attack is very rare. Individuals with HZ are more than once likely to have immunocompromised. Immunocompetent patients with herpes zoster-like disease are most likely to suffer from recurrent zosteriform herpes simplex virus infections. HZ is less contagious than varicella.[1-3]

During the course of varicella, VZV transmits from skin and mucosal lesions to sensory nerve endings and settling in sensory ganglion in periods of latent infection that persist throughout life. The reactivation mechanism is not completely clear, but is suspected to be associated with immunosuppression, emotional stress, radiation, tumor, local trauma, spinal manipulation of the spine, sinusitis. The important thing is the decline in cellular immunity that occurs in old age. Once the virus multiplies and spreads in the ganglion, neuronal and inflammatory necrosis occurs, often accompanied by severe neuralgia and neuritis, and then a distinctive lesion of the skin appears in the form of vesicles. Pain is the main symptom of HZ, which is felt before and during skin symptoms appear, and often persists after the rash is gone. Damage to neurons in the spinal cord and ganglion, and peripheral nerves, is important in the pathogenesis of PHN.[1,3]

Complications of HZ include skin complications (secondary infection, scar, gangrene, cutaneous spread), visceral complications (pneumonitis, hepatitis, encephatilis, gastritis, pericarditis, cystitis, arthritis), neurological complications (postherpetic neuralgia/PHN, meningoencephalitis, transverse myelitis, peripheral paralysis, motor, autonomic, cranial nerves palses, sensory impairment, deafness, Ramsay Hunt syndrome, eye complications, granulomatous angiitis).[1,2,3] A common complication and should be aware of herpes zoster is PHN, which is the pain that settles in the affected dermatome after the eruption of the skin disappears. The incidence of PHN averages about 10-40% .[3] But PHN is more common in elderly than children and adolescents.[1] From 2232 HZ patients in 13 Teaching Hospitals in Indonesia in 2100-2013, 595 (26.5 %) suffered from PHN, and age at most 45-64 years (42%).[3] Pain of PHN may be intermittent pain, and

pain occurs after stimulation, including allodynia (pain due to stimuli that under normal conditions do not cause pain). Painful disorders can cause sleep disturbances, depression, anorexia, weight loss, chronic weakness, social isolation.[1,2,3]

Along with the widespread use of varicella vaccines has changed epidemiologically. The incidence of varicella decreased significantly and decreased hospital admission rates for vulnerable children[4] and adults due to widespread use of vaccines.[1,5] All of 78 varicella patients (100%) in Universitas Airlangga Teaching Hospital, Surabaya, in 2017, had no history of varicella vaccine. After vaccine use, the Centers for Disease Control (CDC) data from 1995-2000 showed that there was a decrease in the number of varicella cases by 71-84%, even in 2005 decreased by 90%. The largest decrease occurred in children aged 1-4 years. The mortality rate also declined from 66% in 1990-1994 at all ages, and the largest decrease of 92% in children aged 1-4 years.[1] The 12-year study in the United States showed that there was a decrease in deaths from varicella after 1 doses of varicella vaccine, with 2 doses proven to decrease severe varicella.[6] Live attenuated varicella vaccine (Oka strain) VZV is immunogenic and effective in protecting vulnerable children. The FDA recommends a combination vaccine of measles, mumps, rubella, and varicella (MMRV) given routinely in children 12 months to 12 years. The Advisory Committee on Immunization Practices (ACIP) recommends two 0.5 ml of varicella vaccine for healthy children ≥12 months, adolescents, adults, without evidence of immunity, at 3-month intervals for 12 months-12 years, 4 weeks for age>13 years old. Single-antigen varicella vaccine is recommended for healthy individuals aged ≥12 months, whereas MMRV is recommended for 12 months - 12 years of age.[1] A prospective study reported vaccine effectiveness 78.9% (95% CI, 69.7-85.3%); for moderate disease prevention 92% (50-500 lesions), and prevention of 100% serious illness. Varicella vaccine is safe, 95% side effects are not serious, mostly mild rash and reaction at the injection site.[1] From 27517 children with varicella, 428 developed into HZ, and it was concluded that children with varicella infections were at greater risk meaningful to get HZ compared to vaccinated children without a history of varicella.[7,8,9] Recommendation of the Ministry of Health of the Republic of Indonesia, the attenuated variance-zoster vaccine may be given with MMR (MMR/V) starting at age of schooling (5 years), in children ≥13 years of vaccine is recommended to be given 2 times a week. Infection after exposure if immunized can occur in 1-2% of cases a year, but the cost of infection is mild. In the case of contact occurs with varicella, for vaccine prevention can be given within 72 hours after transmission (with contact requirements disconnected/unrelated). Contraindications to the vaccine are high fever, leukocyte <1200/ul, or there is evidence of cellular immune deficiency, receiving high-dose corticosteroid therapy (2mg/kgBB per day or more), and gelatin and/or neomycin allergy. The dose is 0.5 ml injections subcutaneously as a single dose.[10] Recommendation of Indonesian Pediatric Association (IDAI) in 2014 on immunization schedule of children aged 0-18 years, varicella vaccine administration given once from 12 months to 18 years old, best given at age before entering elementary school. If given at age> 12 years need 2 doses with interval 4 weeks.[10]

Prevention of HZ can be through by vaccination in parents and individuals at high risk. Live attenuated virus zoster vaccine decreases half the incidence of herpes zoster and two thirds of PHN.[1] Research on individuals aged over 55 years with a history of varicella proven to increase specific T lymphocytes and humoral immunity after vaccination with live attenuated VZV, and proven to reduce the incidence and or severity of HZ and PHN in older people. Vaccine side effects are usually rare and mild.[1] All of 34 varicella patients (100%) in Universitas Airlangga Teaching Hospital, Surabaya, in 2017, had no history of varicella-zoster vaccine. The study from May 2005 to September 2009 on 322 subjects <18 years of age, showed in children given varicella vaccine, the incidence of HZ was 79% lower with the majority of mild types than children not vaccinated.[7] A surveillance proves that varicella vaccine has not been proven cost-effective in preventing HZ as decreasing varicella. Varicella vaccine has not been shown to provide long-term protection against HZV infection, so HZV vaccine is still needed.[11,12] In October 2013, the ACIP reviewed HZ epidemiology and its complications, the availability of HZ vaccine, short-term efficacy at 50-59 years of age, short-long at age ≥60 years, analyzing cost-effectiveness, deliberation in ACIP, and recommending that herpes zoster vaccine be recommended for routine delivery at age ≥60 years.[13] Herpes zoster vaccine is intended to prevent HZ by increasing the body's resistance to VZV. This vaccine should be given to prevent disease, ease the burden of disease, and reduce the occurrence of complications of PHN. The HZ vaccine contains 19,400 plaque units of per-dose, 14 times more virions than varicella vaccines. The recommendation of the Study Group of Herpes Indonesia (KSHI) of this vaccine is given once at age ≥ 50 years.[3]

Noteworthy is the immunocompromised patient. There was fatal disseminated varicella zoster infection with multiorgan failure following HZ vaccination in a 70-years-old man with chronic lymphocytic leukaemia who had been under immunosuppressive regime.[14] It have be found that patients taking immunosuppressant medications at the time of vaccination had a modest increased risk of herpes zoster in the 42 days after vaccination. It suggests that this is more likely due to reactivation of latent zoster virus than dissemination of the vaccine-derived varicella virus.[15]

The Advisory Committee on Immunization Practices recommends the use of HZ vaccines. On October, 2017, Zoster Vaccine Recombinant (ZVR), Adjuvanted (Shingrix, GlaxoSmithKline, [GSK] Research Triangle Park, North Carolina), a 2-dose, subunit vaccine containing recombinant glycoprotein E in combination with a novel adjuvant ($AS01_B$), was approved by the Food and Drug Administration for the prevention of herpes zoster in adults aged ≥50 years. The vaccine consists of 2 doses (0.5 mL each), administered intramuscularly, 2–6 months apart. On October 25, 2017, the Advisory Committee on Immunization Practices (ACIP) recommended the recombinant zoster vaccine (RZV) for use in immunocompetent adults aged ≥50 years. Zoster Vaccine Live (ZVL) (Zostavax, Merck and Co., Inc., Whitehouse Station, New Jersey), a 1-dose live attenuated strain of VZV, is licensed for the prevention of herpes zoster in immunocompetent adults aged ≥50 years and is recommended by the ACIP for use in immunocompetent adults aged ≥60 years. Since licensure, vaccine coverage has increased each year, and by 2016, 33% of adults aged ≥60 years reported receipt of the vaccine (CDC, provisional unpublished data). ACIP considered use of RZV, as well as existing recommendations, to

develop vaccination policy which would be safe and reduce disease burden. This report serves as a supplement to the 2008 Prevention of Herpes Zoster Recommendations of ACIP for the use of ZVL in adults aged ≥60 years and subsequent updates; it outlines recent ACIP recommendations as well as guidance for use of RZV and ZVL in adults.[16] Adults with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease) should receive recombinant zoster vaccine (RZV). As with ZVL, the ACIP recommends the use of RZV in persons taking low-dose immunosuppressive therapy (e.g., <20 mg/day of prednisone or equivalent or using inhaled or topical steroids) and persons anticipating immunosuppression or who have recovered from an immunocompromising illness. Whereas RZV is licensed for all persons aged ≥50 years, immunocompromised persons and those on moderate to high doses of immunosuppressive therapy were excluded from the efficacy studies (ZOE-50 and ZOE-70), and thus, ACIP has not made recommendations regarding the use of RZV in these patients; this topic is anticipated to be discussed at upcoming ACIP meetings as additional data become available. RZV should not be administered to persons with a history of severe allergic reaction, such as anaphylaxis, to any component of this vaccine. Precaution for current herpes zoster infection: RZV is not a treatment for herpes zoster or postherpetic neuralgia and should not be administered during an acute episode of herpes zoster. There are no available data to establish whether RZV is safe in pregnant or lactating women and there is currently no ACIP recommendation for RZV use in this population. Consider delaying vaccination with RZV in such circumstances.[16]

CONCLUSION

Varicella is an acute disease caused by VZV infection that is common in children, whereas herpes zoster is more common in elderly, but it can be suffered by children. Although in normal children the symptoms of varicella and herpes zoster are usually mild but if not managed properly there can be dangerous complications. Comprehensive management is needed to reduce morbidity and mortality of varicella and herpes zoster, including antiviral therapy and prevention by vaccination. Varicella-zoster vaccines have been proven decreasing varicella-zoster infections, decreasing morbidity and mortality complications due to varicella-zoster infections. Varicella-zoster vaccines are safe with minor tolerable side effects, with special condideration in some vulnerable people.

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